PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): PETER WILLIAM SURMAN

Serial No: 10/561,930 Group Art Unit: 1618

Filed: 05-23-2006 Examiner: VU, JAKE MINH

Att. Docket No.: D2026/20001 Confirmation No.: 3207

For: STABLE CLOZAPINE SUSPENSION FORMULATION

DECLARATION OF SHARON FERGUSON UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Sharon Ferguson, a citizen of New Zealand, hereby declare and state:

1. I am a co-inventor of the subject matter described and claimed in the present application.

2. I am the Senior Research Officer, New Product Development, with Douglas Pharmaceuticals Limited ("Douglas"), the assignee of the present application.

3. I have reviewed the present application and its prosecution history including the Office Action of March 1, 2010.

4. I understand that the application presently claims a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11.

5. I understand from my review of the Office Action that the claims currently stand rejected under 35 U.S.C. §103(a) as being unpatentable over Eishun (JP 10-175865) in view of Honma et al (US 6,569,903), Ali et al (US 5,521,222) and Horlington (US 4,425,346).

6. I understand from the attorneys for Douglas that 35 U.S.C. § 103(a) provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

7. While I am not an expert in patent law, my experience and educational background enable me to render an informed opinion as to the facts underlying the determination of obviousness, including: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results. For the reasons discussed below, I believe that the facts support a conclusion that the claims are not obvious over the cited references.

8. I also understand from the attorneys for Douglas that in the Interview conducted May 18, 2010, the Examiner cited the reference Ramuth et al. Pharm Journal 257:190-191, 1996.

9. Based on my review of the reference, I understand that this reference discusses compounding clozapine into liquid preparations using Guy's Pediatric Base.

10. I and/or researchers under my direct supervision were unable to obtain a quantitative formulation for Guy's Pediatric Base, and therefore were unable to test it for stability.

11. However, I and/or researchers under my direct supervision prepared a clozapine liquid preparation using Clatterbridge Hospital Base, which contains 1% xanthan gum and water, but no buffers or preservatives. Clopine 100 mg Tablets (CS 116) and also Clozaril 100 mg Tablets - Australian Ref Product (CS117) were ground and put into the Clatterbridge Hospital Base. These samples were stored them at both 5°C and 40°C, and a Relative Humidity of 75%.

12. The description and pH were noted. The results obtained were:

Storage	Test	CS116	CS117
Time zero	Description; pH	A yellow suspension; pH 7.2	A yellow Suspension; pH 7.2
1 M 40/75	Description	Yellow crystals observed, bad odour.	A yellow suspension, bad odour
1 M 5 degrees	Description	A yellow suspension	A yellow gel formed

2 M 40/75	Description; pH	Not performed	A yellow suspension, bad odour; pH 6.2

13. The Results show that both the CS 116 and 117 samples had a bad odor after 1 month at 40°C and 75% Relative humidity. CS 116 formed crystals after 1 month at 40°C and 75% Relative humidity and no further testing was performed. CS117 after 2 months at 40°C and 75% Relative humidity had a pH drop and a bad odor.

14. As a comparison, using the methods described in the application, I and/or researchers under my direct supervision prepared a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11.

15. Four batches of Clozapine 50 mg/ml Suspension were placed into a stability testing program as shown in the Stability Summary and Conclusions Document attached as Exhibit A.

16. Batches 17298, 17359 and 17361 were the registration batches. Batches 23283 and 32126 are commercial batches that have been scaled up to 1000 L.

17. All five batches of Clozapine 50 mg/ml Suspension were packed in amber glass bottles (type 3) fitted with child resistant, tamper evident caps.

18. Stability results obtained show acceptable stability up to 24 months at 25°C/60 % RH and 6 months 40°C/75 % RH for all batches. (See Exhibit A at page 8). Tabular summaries of the results are located in Appendix 2 of the document presented in Exhibit A.

19. Accordingly, the claimed composition is significantly more stable than would be expected for a clozapine liquid solution preparation.

20. In addition, the claimed physicochemically stable aqueous composition for oral administration comprising clozapine in suspension as manufactured by Douglas has been approved for sale in Ireland. Attached as Exhibit B is the Product Authorization as approved by the Irish Medicines Board.

21. The stable aqueous composition for oral administration comprising clozapine in

suspension has been approved for labeling with a stability of 2 years (i.e., 24 months) (see Exhibit B at page 21).

22. Accordingly, the claimed composition is significantly more stable than would be expected for a clozapine liquid preparation prepared according to the combination of the Eishun, Honma, Ali, Horlington references. In addition, the claimed composition is significantly more stable than would be expected for a clozapine liquid solution preparation.

* * *

23. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 06 August 2010

S Ferguson

Sharon Ferguson